

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
1,3-DICHLOROPROPENE (TELONE II)
Chemical Code # 000573, Tolerance # 50046
SB 950 # 137

August 18, 1986

Revised 4/16/87, 7/18/88, 5/23/89, 4/27/90, 6/1/90, 6/15/94, 8/10/94, 5/01/96,
3/11/97, and 9/23/99

I. DATA GAP STATUS

Chronic, rat:	No data gap, possible adverse effects
Chronic, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, possible adverse effects
Oncogenicity, mouse:	No data gap, possible adverse effects
Reproduction, rat:	No data gap, no adverse effects
Teratogenicity, rat:	No data gap, no adverse effects
Teratogenicity, rabbit:	No data gap, no adverse effects
Gene mutation:	No data gap, possible adverse effect
Chromosomal effects:	No data gap, no adverse effect
DNA damage:	No data gap, possible adverse effect
Neurotoxicity:	Not required at this time

Note, Toxicology one-liners are attached

All relevant record numbers indexed as of 9/9/99 were examined. This includes record numbers up to 169270 (Document No. 50046-139), as well as some older records of the 900,000+ series. Aldous, 9/10/99.

In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T990923.wpd

Original Summary was prepared by F. Martz. Revisions in 1987 to 1990 were by J. Gee. The current revision is by C. Aldous.

See also "Guidance for the Reregistration of Pesticide Products (Reregistration Standard) Containing 1,3-Dichloropropene (Telone II) as the Active Ingredient", US EPA, 9/18/86, DPR Record # 050620. The position of EPA (1986) was that if significant residues were found, oral studies would be required in addition to existing inhalation studies. This appears to explain the presence of recent dietary chronic studies in rat, mouse, and dog, even though acceptable inhalation studies were previously performed in the rodents. Document No. 50046-116 contains a chapter from the 1997 U.S. EPA RED on 1,3-dichloropropene. Gee, 5/23/89, updated by Aldous, 4/23/96.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED RAT (and supporting studies)

****50046-098 140562** Stott, W. T., K. A. Johnson, T. K. Jeffries, K. T. Haut, and S. N. Shabrang, "Telone*II Soil Fumigant: Two-year chronic toxicity/oncogenicity study in Fischer 344 rats". The Toxicology Research Laboratory, The Dow Chemical Co., Midland MI, 8/15/95. Laboratory Project Study ID: M-003993-031. Microencapsulated Telone*II, purity 95.8% 1,3-dichloropropene (50.7% cis/45.1% trans), was admixed with the diet at 0, 2.5, 12.5 or 25 mg/kg/day and fed to 50 F344 rats/sex/group for 24 months. Additional rats (10/sex/group) were allocated for a 1-yr interim sacrifice. No definitive NOEL is present in this study: hepatocellular eosinophilic foci appear increased in number and/or degree at all dose levels. Characteristic findings at 12.5 to 25 mg/kg/day include forestomach basal cell hyperplasia, reduced body weight, and reduced food consumption. Hepatocellular tumors (primarily adenomas) were significantly elevated in high dose males, and non-significantly elevated in mid-dose males and high dose females. The 1996 DPR review noted an apparent elevation in uterine endometrial stromal polyps in 25 mg/kg/day females, however supplemental data in Document No. 50046-104, Record No. 151747 present historical control data which do not support a treatment effect. A number of other changes (particularly reductions in degree or incidence of normal aging lesions) indicate altered physiology or nutritional status influencing the progress of normal geriatric changes in high dose rats. Study is **acceptable**. Liver tumors are "possible adverse effects". Kishiyama and Aldous, 4/19/96; Aldous, 3/11/97.

50046-072 126522 This 116-page report is the 1-yr interim report of Record # 140562 above. There is no essential new information in this report, hence no worksheet. Aldous, 7/15/99.

****50046-073 126523** Haut, K. T., K. A. Johnson, S. N. Shabrang, and W. T. Stott, "Telone II soil fumigant: 13-week dietary toxicity and 4-week recovery studies in Fischer 344 rats", The Dow Chemical Co., Midland, 1/8/93. Laboratory Project Study ID: M-003993-028. Fischer 344 rats, 20/sex/group, were dosed with 0, 5, 15, 50, or 100 mg/kg/day 1,3-dichloropropene in diet (test article was microencapsulated in spheres composed of an 80%/20% starch/sucrose matrix). All rats were exposed for 13 weeks, at which time 10/sex/group were sacrificed, whereas the remaining 10/sex/group were maintained off treatment for 4 weeks to evaluate recovery. The NOEL for toxic endpoints is 5 mg/kg/day (dose-related non-glandular stomach basal cell hyperplasia at 15 mg/kg/day and above). Small but statistically significant decrements in body weight at 5 to 15 mg/kg/day in males and 15 mg/kg/day in females were plausibly treatment-related, but of unlikely toxicological significance (small degree of change or nearly flat dose-response curve). **No adverse effects. Acceptable.** Aldous, 9/21/99.

**** 031, 005 060677, 036218** "Telone II Soil Fumigant: 2-Year Inhalation Chronic Toxicity-Oncogenicity Study in Rats." (Dow Chemical, Midland, MI, 7/13/87, M-003993-009R) 1,3-Dichloropropene, 92.1% (cis 49.5% and trans, 42.6%) stabilized with soybean oil; 70 F344 rats/sex/group exposed by inhalation 6 hours/day, 5 days/week for 2 years - whole body exposure - at 0, 5, 20 or 60 ppm nominal; 10/sex/group sacrificed at 6 and at 12 months (interim report, # 036218); NOEL = 20 ppm (decreased weight gain, changes in nasal tissues in males and females), no evidence of an oncogenic effect reported; ACCEPTABLE with possible adverse chronic effects (erosions of olfactory epithelium, nasal submucosal fibrosis). (Gee, 7/11/88).

50046-005 036218 1 year interim report of Record No. 060677, above.

010 036552 "Toxicology and Carcinogenesis Studies of Telone II in F344/N Rats and B6C3F1 Mice." (NTP, Frederick Cancer Research Center, 5/85) Rats, F344 strain; Telone II (1,3-dichloropropene, 87.5% pure) with epichlorohydrin as stabilizer; 50, 25, or 0 mg/kg by oral gavage "3 times a week"; 52/sex/group with an additional 28/sex/group (3 as substitutes) in satellite groups with sacrifices at 9, 16, 21, 24 and 27 months of 5/sex/group. Study scientifically valid but UNACCEPTABLE and not upgradeable due to guideline deviations. Oncogenicity effects: forestomach cancer at 50 mg/kg, liver cancer in males at 25 and 50 mg/kg, trend for thyroid cancer in females, mammary cancer in females at 50 mg/kg with trend at 25 mg/kg, stomach epithelial hyperplasia at 25 and 50 mg/kg. (Reviewed 1/16/86 by Martz).

CHRONIC DOG

****50046-061 117410** Stott, W.T., Stebbins, K. E., Haut, K. T., Quast, J. F., and Shabrang, S. N.; "Telone*II soil fumigant: One-year dietary toxicity study in beagle dogs", The Dow Chemical Co., Midland, Study ID M-003993-024, 7/22/92. Dogs were fed diets containing microencapsulated Telone*II at 0, 0.5, 2.5, or 15 mg/kg/day for 1 year. NOEL = 2.5 mg/kg/day [hematology profile typical of hypochromic, microcytic anemia: related to increased hematopoiesis in bone marrow and extramedullary hematopoiesis in spleen in both sexes]. Clinical signs in 2 high dose males of pale skin/mucous membranes apparently reflected the anemia. Body weights were depressed and relative liver weights were increased in both sexes at 15 mg/kg/day. The relatively low NOEL for signs of anemia constitutes a "**possible adverse effect**". **Acceptable**; Aldous, 11/15/93.

ONCOGENICITY, MOUSE

**** 029, 006 060675, 036219** "Telone II Soil Fumigant: 2-Year Inhalation Chronic Toxicity-Oncogenicity Study in Mice." (Dow, 7/13/87, M-003993-009) 1,3-Dichloropropene, 92.1% (cis 49.5% and trans, 42.6%) lot TB831213-4; given by inhalation at 0, 5, 20 or 60 ppm nominal uncorrected for 92% purity, 6 hours/day, 5 days/week for 2 years; 70/sex/group with intermediate sacrifices of 10/sex/group at 6 months and at 12 months (interim report # 036219 in 006); daily analytical data for 1,3-dichloropropene concentration. Hyperplasia of the urinary bladder mucosa was found in females at 20 and 60 ppm and in males at 60 ppm with a trend at 20 ppm. Increase in benign lung bronchioalveolar adenomas in males at 60 ppm. Degeneration of the olfactory epithelium and hyperplasia of the respiratory epithelium, bilateral, at 60 ppm in both sexes. Decreased liver vacuolation in females at 60 ppm. NOEL = 5 ppm. ACCEPTABLE with possible adverse effects. (Gee, 7/12/88).

006 036219 (1 year interim report for Record No. 060675, above)

****50046-097 140561** Redmond, J. M., K. E. Stebbins and W.T. Stott, "Telone*II Soil Fumigant: Two-year dietary chronic toxicity/oncogenicity study in B6C3F1 Mice - Final Report", The Toxicology Research Laboratory, The Dow Chemical Co., Midland MI. Aug. 9, 1995. Study ID M-003993-032. Microencapsulated Telone*II, purity 95.8% 1,3-dichloropropene (50.7% cis/45.1% trans), was admixed with the diet at concentrations of 0, 2.5, 25, or 50 mg/kg/day and fed to 50 B6C3F1 mice/sex/group for 24 months. Additional mice (10/sex/group) were allocated for a 1-yr interim sacrifice. NOEL = 2.5 mg/kg/day (body weight decrements, both sexes). Upper dose levels achieved, but did not exceed, an MTD. The most definitively treatment-related effect was decreased hepatocyte size in 6/10 of the 50 mg/kg/day males at 1-yr sacrifice. There was a small increase in high dose females with stromal cell sarcomas, originating in the cervix or uterus, compared to concurrent controls (one control vs. four high dose females). In the 1996 DPR review, this was considered as a "possible adverse effect", and histopathological examinations of cervix or uterus slides of intermediate groups were requested, in addition to relevant historical control data. The requested data were submitted (Document No. 50046-103, Record # 151706). Stromal cell sarcoma incidence was 1, 0, 1, and 4 in controls through high dose groups. Historical control incidence of combined uterine or cervical stromal cell sarcomas ranged from 0 to 4, with 4/16 studies having either 3 or 4 such tumors out of 50 mice. **No adverse effect:** data do not indicate a treatment effect on tumor incidence. The study is now **acceptable as an oncogenicity study** (absence of blood chemistry precludes acceptance as a "combined" study). Aldous, 4/17/96, 3/10/97.

50046-072 126521 This 75-page interim report relates to Record # 140561 above. There are no essential data unique to this interim report. Aldous, 7/15/99.

****50046-074 126524** Haut, K. T., K. E. Stebbins, S. N. Shabrang, and W. T. Stott, "Telone II soil fumigant: 13-week dietary toxicity study in B6C3F1 mice", The Dow Chemical Co., Midland, 1/8/93. Laboratory Project Study ID: M-003993-029. Mice, 10/sex/group, were dosed with 0, 15, 50, 100, or 175 mg/kg/day 1,3-dichloropropene in diet (test article was microencapsulated in spheres composed of an 80%/20% starch/sucrose matrix). Mice were exposed for 13 weeks in a standard subchronic study design. Decreased size of hepatocytes was observed in all male treatment groups ("very slight" degree in all cases): this was attributed by the authors to a decrease in glycogen content. No comparable findings were reported in females. A NOEL for body weight decrements was 15 mg/kg/day for both sexes. Decreased circulating triglyceride levels were found in 100 to 175 mg/kg/day females. All findings were consistent with reduced nutritional status, thus no target organ toxicity was evident. **Acceptable, with no adverse effects.** Aldous, 9/20/99.

VARIOUS MOUSE ONCOGENICITY STUDIES: NON-GUIDELINE EXPOSURE PROTOCOLS

010 036553, "Toxicology and Carcinogenesis Studies of Telone II in F344/N Rats and B6C3F1 Mice." (NTP, Frederick Cancer Research Center, 5/85) Mice, B6C3F1 strain; Telone II (87.5% 1,3-dichloropropene); 100, 50, or 0 mg/kg/day by oral gavage "3 times a week"; 50/sex/group. UNACCEPTABLE and not upgradeable due to guideline deviations, but scientifically valid for female data. Oncogenicity effects; in females, cancer of urinary bladder at 100 and 50 mg/kg, forestomach and lung at 100 mg/kg; results in males inconclusive due to inadequate randomization and poor control group survival. (Martz, 1/17/86).

NOTE: Document No. 50046-010, Record No. 036554 refers to the same published article in JNCI 63 cited in Document No. 50046-007, Record Nos. 028361-028363. Multiple record

numbers in Document No. 50046-007 represent 3 different dosing protocols presented in the publication, none of which approached guideline procedures. Aldous, 4/22/96.

010 036554 "Carcinogenicity of Halogenated Olefinic and Aliphatic Hydrocarbons in Mice." (Van Duuren, B. L. et al., NYU Med Center, JNCI 63: 1433-1439, 1979) Ha:ICR Swiss strain; cis-1,3-dichloropropene (Chemical Samples Co., Columbus, OH), 122 mg/mouse or 41 mg/mouse by dermal application 3/week for about 77 weeks; initially reviewed as having caused no local or distant tumors. UNACCEPTABLE and not upgradeable. Reviewed: 6/3/85 by Apostolou, peer review 2/20 and 8/18/86 by Martz. Re-review as part of the risk assessment process noted that the incidence of lung tumors in both groups of treated mice was statistically significant by Fisher's Exact Test although not so noted in the publication table. The incidences were 30/100 for controls and 19/30 and 17/30 at low and high doses respectively. Study remains UNACCEPTABLE but with a possible adverse effect. (Gee, 5/31/90).

50046-007 028361 (same publication as 036554, above, refers to the repeated dermal cis-1,3-dichloropropene treatments). Reviewed under this record number by Apostolou (see above).

010 036554 "Carcinogenicity of Halogenated Olefinic and Aliphatic Hydrocarbons in Mice." (NYU Med Center, JNCI 63: 1433-1439, 1979) Ha:ICR Swiss strain; cis-1,3-dichloropropene (Chemical Samples Co., Columbus, OH), 3 mg/mouse once weekly x 77 weeks by subcutaneous injection; examined injection site and liver only; fibrosarcoma at injection site, 6/30 vs. 0/30 vehicle control, probably due to irritation by physical-chemical properties of A.I. Otherwise, insufficient for assessment. UNACCEPTABLE and not upgradeable. (Apostolou, 6/3/85; Martz 2/20 and 8/18/86).

50046-007 028362 (same publication as 036554, above, relating to subcutaneous cis-1,3-dichloropropene treatment). Reviewed under this record number by Apostolou (see above).

010 036554 (suppl. to 028363) "Carcinogenicity of Halogenated Olefinic and Aliphatic Hydrocarbons in Mice." (NYU Med Center, JNCI 63: 1433-1439, 1979) Ha:ICR Swiss strain; cis-1,3-dichloropropene (Chemical Samples Co., Columbus, OH), 122 mg/mouse by a single dermal application, followed by promotion with 5 mg phorbol myristate acetate (PMA) dermally 3/week for about 77 weeks; no significant increase in tumors due to the a.i. [4/30 with dermal papillomas in cis-1,3-dichloropropene group: 6/90 in PMA positive control group: 0/100 in untreated mice, and evidently 0/30 in acetone (sham promoter) treatment group]. UNACCEPTABLE and not upgradeable. (Reviewed: 6/3/85 by Apostolou, peer review 2/20 and 8/18/86 by Martz).

50046-007 028363 (relates to investigation using single dermal application of cis-1,3-dichloropropene plus PMA promotion in Record No. 036554, above: originally reviewed under this record number by Apostolou).

SUBCHRONIC STUDIES

038 071713 "Telone II Soil Fumigant: A 13-Week Inhalation Study in Rats and Mice." (Dow, 11/30/84) Telone II, 90.9%, lot WP-82-1111-56; given by inhalation 6 hr/day, 5 day/week, 10 Fischer 344 rats per sex, exposed to 0, 10, 30, 90 or 150 ppm nominal; 13-week exposure; only findings were degeneration in the olfactory epithelium and hyperplasia of the respiratory epithelium in both sexes, especially at 90 and 150 ppm; body weight gains were significantly

lower at 90 and 150 ppm; NOEL = 10 ppm based on hyperplasia in 2/10 males at 30 ppm. Supplementary data. (Gee, 5/22/89).

10 036551 "90-Day Inhalation toxicity Study in Rats and Mice." (Hazleton, (VA), 5/79) CD-1 strain; Telone II, purity unspecified; 90, 30, 10, or 0 ppm 6 hours/day x 5 days/week x 13 weeks (65 exposures). Unacceptable and not upgradeable - was intended as range finder for future study. EFFECTS: In 90 ppm females - epithelium of dorsal nasal septum and turbinates - decreased cytoplasm and single cell necrosis; slight weight gain reduction at 90 ppm; NOEL = 30 ppm. (Martz, 4/29/86).

038 071713 "Telone II Soil Fumigant: A 13-Week Inhalation Study in Rats and Mice." (Dow, 11/30/84) Telone II, 90.9%, lot WP-82-1111-56; given by inhalation 6 hr/day, 5 day/week, 10 B6C3F1 mice per sex, exposed to 0, 10, 30, 90 or 150 ppm nominal; 13-week exposure; findings were degeneration in the olfactory epithelium and hyperplasia of the respiratory epithelium in both sexes, especially at 90 and 150 ppm; body weight gains were significantly lower at 90 and 150 ppm; females in 90 and 150 ppm showed effects in the epithelial cells of the urinary bladder; NOEL = 30 ppm. Supplementary data. (Gee, 5/22/89).

046 075537 "Telone II: 13-Week Dietary Toxicity Study in Beagle Dogs." Quast, J. F., Dow Chemical Company, August 1, 1989. The 3-page letter was submitted as an adverse effects disclosure for microcytic hypochromic anemia in the 13-week study in beagle dogs. Doses were 0, 130, 380 or 1000 ppm with Telone II incorporated in a starch sucrose matrix and administered in the dog chow. The letter contains no data but states the anemia was dose-related. Some dogs were being maintained after dosing for further study. The final report has not yet been received by CDFA. (Gee, 4/27/90).

50046-043 protocol (dated 4/12/89) for the 13-week dietary dog study (see Record No. 075537, above). (Gee, 5/23/89).

50046-094 138953 DowElanco reported as FIFRA 6(a)(2) "possible adverse effect" data on 6/20/95 that they had learned that a European 1,3-dichloropropene product (using soybean epoxide as stabilizer, but not a product sold in the United States) elicited stomach lesions considered to be preneoplastic in subchronic studies. The memo noted that Sprague-Dawley rats administered 25 mg/kg/day or more daily for 28 days had squamous cell hyperplasia and hyperkeratosis in the forestomach (NOEL = 5 mg/kg/day). Also, CD-1 mice had mild cases of hyperplasia and hyperkeratosis in the forestomach at 200 mg/kg/day after 28 days of treatment (lower doses were included in the study, but not evaluated as of the time of the memo). One of 3 attachments was not otherwise included in the present Summary of Toxicology Data: a Dec. 8, 1989 peer review of Telone II cited several tumor types observed following telone treatment, including forestomach tumors. One contributing document to that peer review was the May 1985 NTP study employing F344 rats and B6C3F1 mice, both of which acquired forestomach tumors, as noted elsewhere in this Summary. No DPR review, since there were no fundamentally new reviewable data. Aldous, 9/9/99.

REPRODUCTION

** 030 060676 "Telone II Soil Fumigant: Two-Generation Inhalation Reproduction Study in Fischer 344 Rats." (Dow Chemical, 7/13/87, M-003993-015) 1,3-Dichloropropene, 91.2%, lot #TB831213-4; exposures of 0, 5, 20 or 60 ppm for 7 days increased to 0, 10, 30 or 90 ppm on day 8, 6 hours/day, 5 days/week, two generations, two litters each; 30/sex/group; maternal

animals removed from chamber after gestation day 20 until day 4 postpartum when separated from pups for the 6 hours exposure; parental NOEL = 30 (decreased weight gain, nasal tissue changes at 90 ppm), reproduction NOEL \geq 90 ppm (no adverse effect on reproduction parameters); ACCEPTABLE. (Gee, 7/13/88).

010 036555 "D-D: A 10 Week Inhalation Study of Mating Behavior in Male and Female Rats." (Shell (UK), 4/80) Wistar strain; technical D-D ("epidemiology-chlorohydrin free"), 53.7% 1,3-dichloropropene, remaining constituents mainly chlorinated isomers/analogues; 96, 32, 14, or 0 ppm for 6 hours/day x 5 days/week; treated males mated with naive females after 2, 4, 7, and 10 weeks exposure; treated females mated with naive males after 10 weeks exposure; hematology, serum chemistry, urinalysis, and histopathology on satellite animals; 30 males and 24 females per group with 20 and 15 respectively for reproduction performance and the remainder for hematology, etc. UNACCEPTABLE and not upgradeable: only 1 generation and inadequate group sizes. Otherwise, appears to be a well conducted and documented study with scientifically valid results. NO reproductive effects. Liver and kidney weight elevation at 96 ppm, reversible upon withdrawal, except female kidney values. (Martz, 2/20/86)

TERATOLOGY, RAT

** 010 036561 "Telone II: Inhalation Teratology Study in Fischer 344 Rats and New Zealand White Rabbits." (Dow, 10/83) F344 strain; Telone II (1,3-dichloropropene; 90.1% pure); 120, 60, 20, or 0 ppm via inhalation; 30/group. Study and report ACCEPTABLE. NO developmental effects (NOEL = 120 ppm for malformations/developmental effects); maternal NOEL < 20 ppm (reduced maternal weight gain at all 3 treatment levels.) (Martz, 2/21/86).

TERATOLOGY, RABBIT

** 010 036562 "Telone II: Inhalation Teratology Study in Fischer 344 Rats and New Zealand White Rabbits." (Dow, 10/83) New Zealand White; Telone II (1,3-dichloropropene; 90.1% pure); 120, 60, 20, or 0 ppm via inhalation; 17 - 24 pregnant rabbits per group. Study OK, but report incomplete: reviewed as upgradeable with submission of historical control data, 2/21/86. The historical control data are in #50619, Document 50046-025. The study has been re-reviewed as ACCEPTABLE, 3/26/87. No developmental effects (NOEL = 120 ppm for malformations); NOEL = 20 ppm for reduced maternal weight gain. (Martz, 2/21/86 and 3/26/87).

GENE MUTATION

Summary: Typically mammalian cell studies have been negative. Some older positive bacterial studies have been reported. There are no recent, standard Ames tests employing modern formulation Telone® II (which does not have mutagenic epichlorohydrin as stabilizer). This is important, because older studies (such as Record No. 036558) which were positive did contain epichlorohydrin. One problem is the volatility of the test material and care must be taken to control samples for this property. From the text of the study with CHO, the flasks were tightly capped and loss of test material should not have been a factor. Overall, as of 9/10/99, there is considered to be a possible genotoxic effect in bacteria unless there are more recent studies using the current test article. Gee, 7/18/88 and 9/10/99.

** 019 042945 "The Evaluation of Telone II Soil Fumigant in the CHO Cell/HGPRT Forward Mutation Assay." (Dow, 2/27/86) CHO/HGPRT assay; Telone II (48.9% cis and 43.2% trans 1,3-dichloropropene); 250, 200, 150, 100, 50, or 0 mM without S9 (3 trials) and 200, 150, 125, 100, 50, or 0 mM with S9 (1 trial). Report complete and study ACCEPTABLE. NO evidence of mutagenicity. (Gee, 7/24/86).

016, **004282** & 004293 "Mutagenicity of 1,3-Dichloropropene using Ames Testing." (Schering AG, summary report 9/82) Formulated mixtures containing 1,3-dichloropropene in addition to various other constituents, were tested for mutagenic activity in the Ames Salmonella Test. Results were conflicting and insufficient for independent assessment. UNACCEPTABLE but upgradeable upon submission of complete report(s). Summary contains statement that positive effects were seen with TA1535 and TA100 but no data. Report contains a statement that the methyl isothiocyanate in the sample tested caused cytotoxicity before the mutagenic effect was detectable. No data. (Reviewed: 6/3/85 by Apostolou, peer review 8/18/86 by Martz and 7/18/88 by Gee).

010 036556 "Mutagenicity of 1,3-Dichloropropene in Bacteria Test System." (Nomura Sogo Res. Inst., 12/78) E. coli strain B/r, Wp 2, Try; 49.8%-cis and 46.3%-trans 1,3-dichloropropene, 5000, 2500, 1000, 500, 250, 100, 25, or 0 mg/plate, \pm S9. Unacceptable and not upgradeable due to design deficiencies. No mutagenic effects reported. (Gee, 2/24/86).

010 036558 "Mutagenicity of 1,3-Dichloropropene in Bacteria Test System." (Nomura Sogo Res. Inst., 12/78) Five Salmonella strains for plate assay; 49.8%-cis and 46.3%-trans 1,3-dichloropropene, 0-5000 mg/plate \pm S9; G46 for host-mediated assay in ICR mice at 30 or 60 mg/kg x 3 times/3 hours. UNACCEPTABLE and not upgradeable: single plates. Significant **Positive response** in several strains indicative of base-pair substitution; negative in host-mediated assay. (Gee, 2/24/86).

No record number "Chemical Mutagenesis Testing in Drosophila. III. Results of 48 Coded Compounds Tested for the National Toxicology Program." (Valencia, R., et al., Environmental Mutagenesis 7: 325 - 348 (1985)) 1,3-Dichloropropene technical, 95.5% was tested with male Canton-S wild-type stock by feeding at 5,570 ppm for 72 hours from soaked filter paper. The males were mated to Basc females for 3, 2 and 2 days. No more than 40 females per parental male were mated from each brood. A total of 6584 tests were performed. The percent lethals were 0.12 for control broods and 0.30 for treated broods - **considered positive by the authors**. The translocation test was negative. No worksheet. [Review done in connection with the risk assessment.] (Gee, 5/31/90).

50046-120 162475 Gollapudi, B. B. and Cieszlak, F. S., "Telone® II Soil Fumigant: Evaluation in an *in vivo* assay for gene mutagens using transgenic Big Blue Mice", The Dow Chemical Co., Midland, 2/10/97. Laboratory Study # K-006409-017. Male Big Blue B6C3F1 mice, 5/group, were dosed by inhalation at 0, 10, 60, or 150 ppm of Telone II® Soil Fumigant, 96% purity, for 10 exposures (5/week over 2 weeks), at 6 hours/day. After an additional 17-day expression period, mice were killed. Each cell of the test mouse had about 40 copies of a shuttle vector carrying the *lacI* gene, the *lacI* promoter, the *lacI* operator, and the *αlacI*Z reporter gene. Mouse tissues (lung and liver) were homogenized, and the DNA was collected, digested, and packaged into phage particles using a proprietary system. The packaged DNA was added to plates containing the *E. coli* host bacteria. Following incubation, investigators counted the numbers of blue plaques compared to the total numbers of plaques as an index of mutations of the *lacI* gene. Blue plaques occur when a defective repressor protein allows transcription of the reporter gene, the product of which cleaves a chromogenic substrate (X-gal) in the medium. Only controls and 150

ppm mice were evaluated. Results showed no increases in mutations in lung or liver. Functional positive control tissues evidently derived from a single mouse, which was treated with five daily doses of 15 mg/kg/day diethylnitrosamine in water 54 weeks before sacrifice. Study is **not acceptable but is upgradeable** (DPR review notes concern about positive control). Aldous, 9/23/99.

50046-111 161855 Exact duplicate of 50046-120 162475, above.

Ancillary gene mutation studies

50046-120 162472 Lawlor, T. E., "Evaluation of 1,3-dichloropropene for mutagenic potential in *Salmonella* in the presence of mouse lung homogenate (S9)", Corning Hazleton Inc. (CHV), 11/26/96. CHV Study ID No. 17037-0-401. *Salmonella typhimurium* TA 100 was the only strain employed in this supplemental mutagenicity study, which evaluated the effects of S9 from mouse lung homogenate and of supplementary GSH in Ames-style reverse mutation plate assays following a 20-minute pre-incubation period in sealed tubes. S9 preparations were prepared from B6C3F1 mice: either controls, or exposed to 1,3-dichloropropene by inhalation (63 ppm, 5 days/wk, 2.5 wks). Preliminary tests with mouse lung S9 preparations with positive control substances benzo(a)pyrene and 2-aminoanthracene found that only the latter increased revertant incidence with mouse lung S9 mix. In studies with mouse lung S9 (whether derived from controls or from 1,3-dichloropropene-treated mice, in either case with or without GSH) there was no increase in revertants due to 1,3-dichloropropene treatment over the survivable range of 75 to 300 µg/plate. Studies without S9 similarly showed no treatment effect throughout the meaningful range. Cytotoxicity was evident between 300 and 600 µg/plate with S9. Studies without S9 found no cytotoxicity at 300 µg/plate, but severe cytotoxicity at 450 µg/plate. Results were thus negative under conditions of study (single strain, single trial, three reps/dose level), suggesting that mouse lung microsomal enzymes did not elicit previously-indicated responses by metabolizing 1,3-dichloropropene to a mutagenic intermediate. Useful supplementary data. Aldous, 9/21/99.

50046-111 161852 Exact duplicate of 50046-120 162472, above.

CHROMOSOMAL EFFECTS

** 010 036560 "Evaluation of Telone II Soil Fumigant in the Mouse Bone Marrow Micronucleus Test." (Dow, 5/85) Telone II (49.5%-cis and 42.6%-trans 1,3-dichloropropene), 380, 115, 38, or 0 mg/kg by oral gavage in CD-1 mice, 5/sex/group, 24 or 48 hour sacrifice. Reviewed 2/25/86 as incomplete but upgradeable with justification of the use of only two sacrifice times. This has been submitted as Record #55630 in 50046-025, based on excretion of 93% within 48 hours. The study is now reviewed as ACCEPTABLE. NO increase in micronucleated PCE's reported. (Gee, 2/25/86 and 4/16/87).

**50046-115 162466 Gollapudi, B. B., F. S. Cieszlak, and S. J. Lick, "Telone* II soil fumigant (cis/trans 1,3-dichloropropene): inhalation dominant lethal mutagenicity study in the CD (Sprague-Dawley derived) rat", The Dow Chemical Co., Midland, 5/29/97. Laboratory Project Study ID 960035. Thirty male Crl:CD®(SD) rats per treatment group were dosed by inhalation for 6 hr/day, 7 days/wk, 10 weeks duration at levels of 0, 10, 60, and 150 ppm. Negative pair-fed controls (matched to food consumption of high dose rats) and positive controls (single oral dose of cyclophosphamide given 48 hr prior to first mating period) were not housed in inhalation chambers. Each of these male treatment groups consisted of 30 rats. There were two

consecutive mating periods of 1 week each during weeks 11 and 12 (1 male/2 females). On day 13 after the end of respective mating periods, females were euthanized. Corpora lutea were counted, and uteri were examined for numbers of live implants and resorption sites. Uteri of apparently non-pregnant females were stained with sodium sulfide and examined for possible early resorptions. The NOEL for "subacute" change = 10 ppm (decreased food consumption and decreased body weight, particularly during the first week of treatment,). There was no evidence of a dominant lethal effect (no increase in resorptions). **Acceptable, with no adverse effects.** Aldous, 8/18/99.

DNA DAMAGE

Summary: Different tests measures different endpoints so no one conclusion can be reached. and a possible adverse genotoxic effect is noted. As was the problem with point mutation studies above, older investigations employing mutagenic epichlorohydrin as stabilizer may not be relevant to evaluation of modern formulation Telone® II. Gee, 7/18/88 and 9/10/99.

**** 010 036559** "Evaluation of Telone II in the Rat Hepatocyte Unscheduled DNA Synthesis Assay." (Dow, 4/85) UDS in rat hepatocytes; Telone II (49.5% cis and 42.6% trans-1,3-dichloropropene) 1×10^{-7} to 3×10^{-3} M concentration (solubility limit), plus control. Report complete and study ACCEPTABLE. NO evidence of UDS even when cytotoxicity was noted. (Gee, 2/24/86).

010 036557 "Mutagenicity Test on 1,3-Dichloropropene in Bacteria Test System." (Nomura Sogo Res. Inst., 12/78) Bacillus subtilis rec assay, strains H17 and M45; 49.8% cis- and 46.3% trans-1,3-dichloropropene, 1250, 500, 125, 50, or 0 mg/well without activation. UNACCEPTABLE and not upgradeable due to design deficiencies. **Slight growth differences at highest level.** Reviewed 2/24/86 by Gee.

50046-119 162470 Stott, W. T., T. J. Miller, and A. K. Wardynski, "1,3-Dichloropropene: *in vitro* DNA binding", The Dow Chemical Co., Midland, 12/12/97. Laboratory Project Study ID 970180. The study evaluated adduct formation when ^{14}C -labeled test material was incubated with calf thymus DNA solution with appropriate co-factors. Functional positive controls were ^{14}C -methyl iodide (without S9) and ^{14}C -1,2-dichloroethane (with S9). ^{14}C -1,3-dichloropropene did not elicit binding with or without S9. Useful ancillary data. The study does not address FIFRA data requirements, and was not performed under QA oversight. Aldous, 9/23/99.

50046-111 161850 Exact duplicate of 50046-119 162470, above.

Note: The reregistration standard of 1986 noted requirements for in vitro/in vivo primary hepatocyte UDS testing both in vitro and in vivo exposure - species not specified. Record # 036559 is not cited. (Gee, 5/23/89).

NEUROTOXICITY

Not required at this time.

GENERAL INFORMATION

007, 932850; Communication to EPA from Dow dated 2/9/82; contains risk assessment based on data from NTP rat and mouse studies (# 036552 & 53) as well as published dermal studies (# 036554), and refers to oncogenic effects noted in the former. (Martz, 8/18/86).

016, 932849, 932853, and 022757; Contain preliminary summary of NTP studies (# 036552 & 53), summary of mutagenicity studies showing positive effects (# 036556-58), and summary of the one generation reproduction study with technical D-D (# 36555), respectively. (Martz, 8/18/86).

50046-016 149370 Brief summaries of toxicology data as of 1982. No reviewable data. Aldous, 3/10/97

50046-139 169270 Rao, K. S., "Telone II: 1,3-dichloropropene (1,3-D): mammalian risk assessment", Final Draft Document submitted to Toxicology Excellence for Risk Assessment (TERA) panel members, Dow AgroSciences, 10/20/98. **Summary makes the following assertions and recommendations:** current production Telone II lacks mutagenic potential under normal physiological conditions. Older formulations had epichlorohydrin as a stabilizing agent, which evidently contributed to mutagenic and oncogenic properties of that material. Current production Telone II lacks epichlorohydrin, and also the associated risks. Dose levels of Telone II high enough to deplete tissue levels of glutathione may elicit oncogenicity (as in rat liver). Often the primary chronic findings are related to local irritant actions of Telone II to mucosal tissues as determined by route (as to the forestomach lining or respiratory tract). Results from exposures to very high dose levels are not representative of plausible human exposures. This assessment concluded that benchmark methodology at the 0.1 level could be used to derive RfC values of $41 \mu\text{g}/\text{m}^3$ for chronic toxicity for mouse nasal epithelial effects, or 80 to $800 \mu\text{g}/\text{m}^3$ for bronchioalveolar adenomas; and RfD values of 0.022 mg/kg/day for male rat forestomach hyperplasia and 0.025 to 0.008 mg/kg/day for liver tumors. If cancer potency data are required to be used based on oncogenicity results, the potency calculations would be $1.3 \times 10^{-5} (\mu\text{g}/\text{m}^3)^{-1}$ and $4.0 \times 10^{-2} (\text{mg}/\text{kg}/\text{day})^{-1}$, respectively.

The above record continues with attachments, as numbered below:

(1) Several communications dating up to 1993 relating to status of Telone II with the European Community partners.

(2) IRIS record for 1,3-dichloropropene dating to 1993.

(3) U.S. EPA Reregistration Eligibility Document (2 Sept. 1997). This document noted that the negative results in the recent inhalation-route dominant lethal assay (Record No. 162466, above) "... lessen the concern for germ cell [mutagenic] effects; therefore, no further mutagenicity testing is required" (p. 10). The HED derived a Q_1^* value of 5.33×10^{-2} in 1994 based on male mouse bronchioalveolar adenomas (p. 13). When the HED RfD Peer Review Committee met in January, 1997 to re-evaluate status of Telone II, they determined that there was no need to change the "carcinogenicity classification" nor the Q_1^* (p. 14), largely due to positive mutagenicity studies which support the "weight-of-evidence" for Telone II as an oncogen.

(4, 5, 6, and 7) These four attachments provide the mathematical analyses for "point of departure" evaluations. For non-cancer effects, Attachment 4 relates to female mouse nasal epithelial hyperplasia and hypertrophy following inhalation exposure (pp. 55 ff. of report), and Attachment 5 relates to male rat forestomach non-glandular mucosal basal cell hyperplasia (pp. 59 ff. of report). For cancer effects, Attachment 6 relates to inhalation exposure in the mouse oncogenicity study (Record No. 060675), in which male mice had elevated bronchioalveolar adenomas at the highest dose level only. This document proposes a benchmark concentration

model (p. 62 of report), however linearized multistage extrapolation analyses are also provided (p. 66 of report). The final cancer evaluation (Attachment 7) relates to male rat liver tumors following oral exposure. Both benchmark and linearized multistage extrapolation analyses were discussed in the report (pp. 68 to 72). Attachments 6 and 7 provided strictly benchmark approach analyses.

Attachments 8 and 9 address dosimetry of inhaled toxicants with respect to respiratory tract anatomy and physiology in order to extrapolate animal data to humans.

The above data do not provide data appropriate for review under SB-950. No worksheet.

Aldous, 7/22/99.

50046-116 162467 DowElanco response to draft HED and EFED RED chapters (relates to 1997 U.S. EPA document on 1,3-dichloropropene). Primary interest for this Summary is the tab: "Response to Tox. Portions - Draft HED RED Chapter". Authors (Stott, W. T. and B. B. Gollapudi) determined that the EPA document made excessive use of outdated studies and applied highly conservative risk extrapolation models. Further, recent mammalian metabolism and mutagenicity studies were often ignored in favor of older *in vitro* studies, hence results often do not have relevance to physiological responses of plausible exposure scenarios. Toxicity studies selected for analyses by U.S. EPA were often bolus-dose treatments, which are known to be able to saturate normal physiological defense mechanisms. Many older studies used obsolete formulations of 1,3-dichloropropene containing up to 2% epichlorohydrin, which is a known mutagenic stabilizing agent not found in current production. Many of the lesions, including tumors, elicited by 1,3-dichloropropene are port-of-entry effects which would not be expected to occur under most plausible exposure scenarios. No worksheet (no "reviewable" data). Aldous, 7/26/99.

50046-117 162468 This is a continuation of 162467, by the same authors. Primary contribution is evidence that 1,3-dichloropropene does not bind to calf thymus DNA *in vitro* nor in liver nor lungs of F344 rat nor in B6C3F1 mice *in vivo*. Liver GSH depletion was shown at gavage doses of 25 to 100 mg/kg/day for 3 days (NOEL = 12.5 mg/kg/day). Lung GSH was dose-related in the range of 10 to 150 ppm (NOEL not sought nor obtained in this study). See Document No. 50046-119 for details. No worksheet for this brief summary record. Aldous, 7/26/99.

50046-118 162469 Calhoun, L. L. "Additional comments in response to the risk assessment portions of the draft HED RED chapter for 1,3-D: November 21, 1997." This brief record states that threshold-based calculations should be used for chronic and oncogenicity findings. Tables therefore present benchmark dose (BMD) analyses for male rat forestomach basal cell hyperplasia and for male rat hepatocellular adenoma. No worksheet (no "reviewable" data). Aldous, 7/26/99.

50046-119 162471 Stott, W. T., B. B. Gollapudi, C. M. Clements, V. A. Linscombe, D. A. Dittenber, S. J. Lick, and K. A. Johnson, "1,3-Dichloropropene: mechanism of tumorigenicity studies in male B6C3F1 and Fischer 344 rats", The Dow Chemical Co., Midland, 12/12/97. Laboratory Project Study ID # 971121. Hepatocellular tumors were noted in male F344 rats administered microencapsulated telone in the diet (Record No. 140562), and benign lung bronchioalveolar adenomas were previously found in male B6C3F1 mice in an inhalation study (Record No. 060675). The present study sought to determine whether telone is mutagenic or otherwise likely to have elicited such tumors by any of several means evaluated, including: (1) cell proliferation studies: evaluated by analysis of BrdU uptake in target tissues, with nuclear labeling visualized by immunohistochemical methods, (2) apoptosis: evaluated by using antibodies to the exposed 3'-OH ends of DNA fragments (which are characteristic of apoptosis), followed by antibody binding, then by addition of a chromophore to the antibody constituents,

allowing quantitation by light microscopy (3) Glutathione (GSH) was evaluated from rat liver and mouse lung homogenates by a clinical chemistry analyzer (in addition to sacrifices of animals exposed continuously up to the time of sacrifice, some rats and mice were killed about 24 hr after the last exposure to assess "rebound" recovery of GSH in tissues), (4) DNA adduct formation was evaluated by a ^{32}P -post-labeling assay, in which DNA was isolated, digested to release 3'-mononucleotides, enriched in certain fractions expected to contain adducts: these fractions were then labeled using T4 polynucleotide kinase and $[\gamma\text{-}^{32}\text{P}]\text{ATP}$, and finally treated with nuclease P1 to create labeled 5'-mononucleotides. Labeled adducts were then separated by 2-dimensional TLC. Chromatograms were compared to those produced by action of a known mutagen (propylene oxide) on DNA samples *in vitro*. NOEL's in rats and mice were 12.5 mg/kg/day and 10 ppm, respectively, based on reductions in GSH levels. NOEL's for outcomes more commonly considered to reflect toxicity, such as modest body weight decrements in both species and increased circulating ALT and AST in rats as indicators of liver responses, were 25 mg/kg/day and 60 ppm, respectively. Evidence of strong dose-response for depletion of GSH and increased turnover of GSH suggest that high dose effects may relate to depletion of natural detoxification capacity, indicating that high dose responses, including tumors, may have little or no relevance to chronic exposure at lower levels. None of the mechanistic studies identified treatment effects on cell proliferation, apoptosis, or DNA adduct formation. The authors concluded that the tumors were caused by a non-genotoxic mode of action *in vivo*. Often, small sample sizes and large inter-animal variability limited the level of confidence in these "negative" results. Aldous, 9/23/99.

50046-111 161851 Exact duplicate of 50046-119 162471, above.

50046-120 162473 Stott, W. T., J. R. Gilbert, R. J. McGuirk, K. A. Brzak, M. D. Dryzga, and M. J. Bartels, "Bioavailability of microencapsulated Telone*II Soil Fumigant in Fischer 344 rats", The Dow Chemical Co., Midland, 8/21/96. Laboratory Project Study ID # M-003993-027. Female rats received 25 mg/kg each of microencapsulated (Midwest Research Institute) and neat telone by gavage in corn oil, prior to sampling the blood for cis and trans isomers over the course of an hour. ^{13}C -telone was used for the neat treatment, whereas the microencapsulated application used the common isotope (^{12}C -telone), allowing investigators to distinguish between modalities of exposure by subsequent mass spectrometry. Microencapsulated telone was quite stable in corn oil, yet gave peak blood concentrations within minutes after gavage administration. Microencapsulated cis- or trans- 1,3-dichloropropene was absorbed as quickly or more quickly than neat administrations of the same isomers. Urinary excretion half-lives were determined. Thus microencapsulation is a viable technique for oral administration. Aldous, 9/7/99 (no worksheet).

50046-111 161853 Exact duplicate of 50046-120 162473, above.

50046-120 162474 Stott, W. T. and H. S. Stewart, "Determination of glutathione transferase activities in several mammalian cell lines", The Dow Chemical Co., Midland, 8/27/96. Laboratory Project Study ID # T2.06-001-014-001. Investigators evaluated activities of glutathione transferase using 4 substrates: racemic ^{14}C -UL-1,3-dichloropropene; 4-chloro-1,3-dinitrobenzene (CDNB); *p*-nitro-phenethylbromide (NPEB); and trans-4-phenyl-3-buten-2-one (TPBO). Sources of GSH transferase activities were rat liver cytosol, mouse liver cytosol, primary rat hepatocytes, CHO cell line, and two Chinese hamster lung cell lines. GSH transferase activities were compared with previously published activities for *Salmonella typhimurium*. GSH transferase activities using ^{14}C -UL-1,3-dichloropropene were about 10-fold higher for the liver 100,000 x g cytosol (rat slightly more active than mouse) compared to

preparations from the three cell lines, and over 1000 times higher than was reported for the bacterial cytosol. Aldous, 9/23/99 (no worksheet).

50046-111 161854 Exact duplicate of 50046-120 162474, above.